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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,281	11/19/1999	JAN BURIAN	660081.411	8461

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
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26

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/444,281	Applicant(s) BURIAN ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,12,13,15-18,20,29,31,32,35-37,40-42,44,45 and 47-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,12,13,15-18,20,29,31,32,35-37,40-42,44,45 and 47-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16&25* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

The Amendment and Response filed 7-16-03 has been entered and considered. Claims 65-67 have been added. Claims 1-2, 4, 12-13, 15-18, 20, 29, 31-32, 35-37, 40-42, 44-45, 47-67 are pending and have been considered on the merits in this Office Action.

Information Disclosure Statement

Applicants noted that reference AD of the Second Supplemental Information Disclosure Statement filed on November 27, 2001 was not initialed as considered by the examiner and requested a copy of the fully initialed IDS. A fully initialed copy of the IDS was faxed on July 7, 2003. However, to insure that a fully initialed copy of the IDS has been received, a copy is attached to this Office Action.

Rejections Withdrawn

The rejection of Claims 1, 2, 4, 16, 17, 18, and 20 under 36 U.S.C. 102(e) as being anticipated by Better et al. is withdrawn in light of the amendment to Claim 1. The encoded protein of Better et al. does not have 30% tryptophan as presently claimed.

The rejection of Claim 15 under 35 U.S.C. 103(a) as obvious over Better in view of Shen et al., Stratagene Catalog, the Pharmacia Product Catalog, and Sambrook et al. is withdrawn in light of the amendment to Claim 1 and for the same reasons as given for the anticipation rejection over Better above.

The rejection of Claims 20 and 50 under 35 U.S.C. 112, second paragraph is withdrawn in light of the amendment to the claims. ****However, the examiner disagrees with Applicants assertion that Claim 50 is not limited to require two indolicidin analogs. Claim 50 depends from Claim 47. Claim 47 is a multiply dependent claim and depends from Claims 29, 37, 41, or 42. Claims 41 and 42 are limited to the expression cassette of Claim 29 wherein n has a value of between 5 and 30 (in claim 41) or n has a value of between 10 and 20 (in claim 42). Therefore, since n describes the number of repeats of the components in the parenthesis including an indolicidin analog, claim 41 is limited to 5-30 indolicidin analogs and claim 42 is limited to 10 and 20 indolicidin analogs. Thus, Claim 50, dependent on Claims 41 or 42 also contains these limitations. ****

The rejection of Claims 41 and 42 under 35 U.S.C. 112, 2nd paragraph is withdrawn in light of the amendments to these claims.

New Rejections Necessitated by Newly Submitted IDS and Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 12, 13, 15, 16, 17, 18, 20, 29, 30, 32, 35-37, 40-42, 44-45, 47-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 29 are indefinite for the recitation of "retain at least 30% tryptophan". Applicants' response implies that the phrase is intended to mean that the "indolicidin analogs" have at least 30% tryptophan. However, the term "retain" means to keep in possession. Therefore, does the claim mean that the analogs have at least 30% tryptophan or that they retain at least 30% tryptophan of the indolicidin peptide? The indolicidin peptide contains 5 tryptophan residues. Therefore, 30% tryptophan of the indolicidin peptide would mean that the claimed peptide has at least two tryptophan residues (rounding up from 1.5). The examiner suggests changing the claim to state "wherein the indolicidin analogs have at least 30% tryptophan".

Claims 2, 4, 12, 13, 15, 16, 17, 18, 20, 30, 32, 35-37, 40-42, 44-45, and 47-67 are rejected since they depend from indefinite Claims 1 and/or 29 and do not correct their deficiencies.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 16, 17, 18, 20, 44, 51, 52, and 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Fraser et al. (WO 98/40401; Ref. AN of IDS filed July 16, 2003).

Fraser et al. teach and claim an expression cassette comprising a promoter operably linked to a nucleic acid molecule that encodes a fusion protein of the structure (indolicidin analog)-[(cleavage site)-(indolicidin analog)]n; wherein n is 1, and wherein the indolicidin analogs have at least 3% tryptophan and have antimicrobial activity. The indolicidin analog MBI 11B20 recited in claim 1 of Fraser et al. has two indolicidin analog sequences separated by a methionine. The two indolicidin peptide sequences of the MBI 11B20 analog are 1) ILRWPWWPWRRK and 2) ILRWPWWPWRRK. The methionine that is positioned between the two indolicidin analog sequences is considered a cleavage site since it may be cleaved by cyanogens bromide. The indolicidin analog MBI 11B20 has antimicrobial activity (p. 46, Ex. 6). The first indolicidin analog of Fraser et al. (the N-terminal analog) has a sequence identical to that of SEQ ID NO:36 and therefore Fraser et al. meets the limitations of Claim 56 (see sequence alignment attached to this Office Action). Claim 10 of Fraser et al. is drawn to an expression vector comprising a promoter in operable linkage with a nucleic acid encoding the indolicidin analog of Claim 1 and therefore Fraser et al. meets the limitations of Claims 1 and 4 (since it can be cleaved with cyanogen bromide) of the present application. Claim 11 of Fraser et al. is drawn to a host cell comprising the claimed expression vector and therefore Fraser et al. meets the limitations of Claim 16 of the present application. Fraser et al. discloses that bacteria and yeast, among other

host cells, may be used to express the disclosed peptides but that expression in E. coli is disclosed specifically therein (see paragraph bridging pp. 15-16). Therefore, Fraser et al. meets the limitations of Claim 18 of the present application. Fraser et al. teaches a method of producing the proteins disclosed therein comprising culturing the recombinant host cell containing the vectors encoding the indolicidin analogs under conditions to produce the peptide (p. 16, first full paragraph) and therefore Fraser et al. meets the limitations of Claim 20. Fraser et al. also teaches fusing the peptides disclosed therein to a carrier protein to transport the fusion peptide to inclusion bodies, the periplasm, the outer membrane or the extracellular environment (p. 16, lines 10-12) and therefore Fraser et al. meets the limitations of Claim 2.

Claims 1, 2, 4, 15, 16, 17, 18, 20, 44, 51, 52, and 56 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieger et al. (U.S. Patent No. 6,503,881; Ref. AD of IDS filed July 16, 2003).

Krieger et al. teach an expression cassette comprising a promoter operably linked to a nucleic acid molecule that encodes a fusion protein of the structure (indolicidin analog)-[(cleavage site)-(indolicidin analog)]n; wherein n is 1, and wherein the indolicidin analogs have at least 3% tryptophan and have antimicrobial activity. The indolicidin analog 11B20 (SEQ ID NO:50) recited in claim 1 of Krieger et al. has two indolicidin analog sequences separated by a methionine. The two indolicidin peptide sequences of the MBI 11B20 analog are 1) ILRWPWWPWRRK and 2) ILRWPWWPWRRK. The first indolicidin analog has a sequence identical to SEQ ID

NO:36 of the present invention and therefore Krieger et al. meets the limitations of Claim 56. The methionine that is positioned between the two indolicidin analog sequences is considered a cleavage site since it may be cleaved by cyanogen bromide. Krieger et al. teaches that the peptides disclosed therein are expressed using an expression vector comprising a promoter in operable linkage with a nucleic acid encoding the indolicidin analog (Col. 17 and Col. 18, lines 1-2) and therefore Krieger et al. meets the limitations of Claims 1 and 4 (since it can be cleaved with cyanogen bromide) of the present application. Krieger et al. teaches that the promoter used in the expression cassette may be the lambda promoter (Col. 18, line 66), the T7, SP6, trp, lpp, tac, trc, and lac promoters (Col. 18, lines 12-15) Krieger et al. teaches that the expression vector disclosed therein is introduced into a host cell (Col. 18, lines 58-67) and therefore Krieger et al. meets the limitations of Claim 16 of the present application. Krieger et al. discloses that E. coli cells may be used to express the disclosed peptides (see Col. 18, lines 58-63). Therefore, Krieger et al. meets the limitations of Claim 18 of the present application. Krieger et al. teaches a method of producing the proteins disclosed therein comprising culturing the recombinant host cell containing the vectors encoding the indolicidin analogs under conditions to produce the peptide (Col. 17-18)) and therefore Krieger et al. meets the limitations of Claim 20. Krieger et al. also teaches fusing the peptides disclosed therein to a carrier protein to transport the fusion peptide to inclusion bodies, the periplasm, the outer membrane or the extracellular environment (Col. 17, lines 20-32) and therefore Krieger et al. meets the limitations of Claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fraser et al. (WO98/40401) or Krieger et al. (U.S. Patent No. 6,503,881) in view of Zhang et al. (Biochem. Biophys. Res. Comm. (1998) 247: 674-680; Ref. AP of IDS of Paper No. 11).

The teachings of Fraser et al. and Krieger et al. have been described above.

Fraser et al. and Krieger et al. do not specifically teach that the expression cassette contains a nucleic acid molecule that encodes a carrier protein of less than 100

amino acids in length or a carrier protein that is a truncated cellulose binding domain of less than 100 amino acids.

Zhang et al. teaches that adding a nucleic acid sequence encoding a truncated cellulose binding domain (CBD_{syn}) of about 36 amino acids (see Fig. 1) stabilized the fusion protein and yielded expression levels higher than analogous constructs that did not contain the CBD_{syn} (see p. 678, paragraph spanning Col. 1-2 and Table 2; construct 1 vs. construct 2).

Therefore, it would have been obvious for one of ordinary skill in the art to modify the expression cassette of Fraser et al. or Krieger et al. by adding a nucleic acid sequence encoding CBD_{syn} as taught in Zhang et al. because Zhang et al. teaches that such a carrier protein helps to stabilize the fusion protein and its presence leads to higher expression; a goal of the Fraser et al. and Krieger et al. research.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fraser et al. (WO98/40401) in view of Shen et al. (Proc. Natl. Acad. Sci. (1984) 81: 4627-4631; ref. BH of IDS of Paper No. 9), Stratagene Catalog (1993; pp38, 44, and 48), the Pharmacia Product Catalog (1996; pp. 110 and 121-123), and Sambrook et al. (Molecular Cloning: A laboratory Manual, 1989, Cold Spring Harbor Laboratory Press, p. 1.14-1.15).

The teachings of Fraser et al. have been described above. Fraser et al. discloses that a promoter is required in the expression cassettes disclosed therein and that the promoters can either be constituitive or inducible (p. 16, last paragraph).

Fraser et al. does not specifically define what promoter should be used in the expression cassette disclosed therein.

Shen et al. teach that lac and tac promoters can be used successfully in the high level expression of proteins from cassettes containing multiple copies of coding sequences.

The Stratagene catalog, Pharmacia catalog, and Sambrook et al. provide evidence that the promoters listed in claim 15 were well known in the art and readily available at the time of the invention.

MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, Shen et al., Sambrook et al., and the Pharmacia and Stratagene catalogs teach that there are a variety of promoters that can be used in the recombinant expression of proteins. As evidenced by Shen et al., Sambrook et al., and the Pharmacia and Stratagene, the promoters of Claim 15 were well known in the art and readily available at the time of the invention. A person of ordinary skill in the art would have recognized the interchangeability of the promoters of Claim 15. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have chosen one of the promoters described in Sambrook et al. and/or described and available in the Stratagene Catalog or the Pharmacia Catalog in the expression cassettes of Fraser et al. One would have had motivation to change the promoter

depending on the materials (host cells, vectors, induction materials such as IPTG) available in the laboratory. Thus, the claims are unpatentable over the prior art.

Applicants' argument that each of the cited references merely provides additional promoters that can be used in an expression is merely cumulative subject matter taught in the instant application and that each cited reference fails to teach or suggest the fusion protein of the present invention.

This argument has been considered but is not deemed persuasive because as stated in the previous Office Action, the selection of known material based on its suitability for its intended use supports the determination of prima facie obviousness. Moreover, the test for obviousness is not whether the claimed invention must be expressly suggested in any or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art (In re Keller, 208 USPQ 871, 881). In the present case, Shen et al., Sambrook et al. and the Pharmacia and Stratagene Catalogs provide promoters that were well known to be used successfully in all kinds of expression vectors. Thus, absent evidence that the claimed expression vector is unusually sensitive to the type of promoter, the claims are obvious over the prior art.

Examiner's Note on the above prior art Rejections

In making the above prior art rejections, the Examiner has considered the Declaration under 37 C.F.R. 1.131 by Burian and Bartfield. The Declaration provides photocopies of laboratory pages from notebooks describing the construction of an

expression vector containing several copies of indolicidin analogs and states that such expression cassettes were conceived prior to 1998. However, the Declaration does not overcome the prior art of Fraser et al. or Krieger et al. because 1) there is no evidence in the laboratory pages that a peptide cleavage site between indolicidin analogs was contemplated; and 2) the expression cassette disclosed in the Declaration and the expression cassette disclosed in the prior art references of Fraser et al. or Krieger et al. are distinct species encompassed within the claimed genus. Thus, the examiner suggests amending the claims to be drawn to the specific expression cassettes disclosed in the Application that are distinct from and do not encompass that of Fraser et al. or Krieger et al. in order to overcome this rejection.

Conclusions

No Claims are allowable.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on July 16, 2003 and Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i) and § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS

Holly Schnizer
October 3, 2003

Christopher S. F. Low

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